

The Effect of Prognostic Factors on Survival in Endometrioid Type Adenocancer

Endometrioid Tip Adenokanserde Prognostik Faktörlerin Sağkalıma Etkisi

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ABSTRACT

Objective: The study aims to investigate the prognostic factors in uterine endometrioid adenocarcinoma that affect survival outcomes.

Materials and Methods: This retrospective study includes 144 cases which underwent surgical treatment for uterine endometrioid adenocarcinoma. Demographic data and tumour characteristics were evaluated for lymph node metastasis. Stage I and grade 1-2 tumours were divided into lymphadenectomy and non-lymphadenectomy groups, and 5-year survival was assessed.

Results: The presence of myometrial invasion of more than 1/2, adnexal metastasis and lymphovascular space invasion were found to be associated with lymph node metastasis ($p=0.010$ ve 0.019 ve 0.015). In our study, the 5-year survival rate was 87.4%. Survival rate was correlated with age, myometrial invasion, and tumour grade. The 5-year survival rates were 89.8% in lymphadenectomy group and 85.2% in non-lymphadenectomy group, and no statistically significant difference was observed ($p=0.575$).

Conclusion: Myometrial invasion, grade and the age of diagnosis were detected as important prognostic factors of uterine endometrioid adenocarcinomas. We concluded that lymphadenectomy did not increase the survival rate of stage I grade 1-2 endometrioid tumours. Lymphadenectomy may not be performed in stage I grade 1-2 tumours; thus, the morbidities of lymphadenectomy can be avoided.

Keywords: Endometrial cancer, lymphadenectomy, prognostic factors

ÖZ

Amaç: Uterusun endometrioid tip adenokanserlerinde prognostik faktörlerin sağ kalıma etkisini saptamayı amaçladık.

Materyal ve Metot: Kliniğimizde 2006 Mayıs- 2012 Mayıs arasında endometrium kanseri nedeniyle cerrahi tedavi uygulanan histolojik tipi Endometrioid Adenokarsinom olan 144 olgu çalışmaya dahil edildi. Demografik veriler ve tümör özelliklerinin lenf nodu metastazı ve sağ kalıma ilişkisi değerlendirildi. Evre I grade 1-2 tümörler lenfadenektomi yapılanlar ve yapılmayanlar olarak gruplandırılarak 5 yıllık sağ kalım değerlendirildi.

Bulgular: Miyometriyal invazyonun $>1/2$ den fazla olmasının, adneksiyal tutulumun ve lenfovasküler alan invazyon varlığının lenf nodu metastazı ile ilişkili olduğu izlenmiştir ($p=0,010$, $0,019$ ve $0,015$). 5 yıllık sağ kalım %87,4 olarak bulunmuştur. Yaş, miyometriyal invazyon ve tümörün grade'nin sağ kalım ile ilişkili olduğu gözlenmiştir. 5 yıllık sağ kalım lenfadenektomi yapılan grupta %89,8, lenfadenektomi yapılmayan grupta ise %85,2 olarak hesaplanmıştır ve aralarında istatistiksel olarak anlamlı bir fark izlenmemiştir ($p=0,575$).

Sonuç: Miyometriyal invazyon, adneksiyal tutulum ve lenfovasküler alan invazyon varlığının önemli birer prognostik faktör olduğunu belirledik. Evre I grade 1-2 tümörlerde lenfadenektominin sağ kalımı arttırmadığını saptadık. Evre I grade 1-2 tümör varlığında lenfadenektomi yapılmayabilir. Böylece lenfadenektominin hastaya yükleyeceği morbiditeden kaçınılabılır.

Anahtar Kelimeler: Endometrium kanseri, lenfadenektomi, prognostik faktör

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INTRODUCTION

Endometrial cancer is the most common malignancy of the female urogenital system in developed countries and the second most common cancer after cervical cancer in developing countries.¹ According to the International Agency for Research on Cancer, 382069 new cases are reported each year.² In the United States, uterine corpus cancer is the fourth most common cancer, and in 2023 approximately 66200 new cases are expected to be reported and 13030 cases to result in death.³

The main risk factor of endometrial cancer is unopposed estrogen. In postmenopausal women, adipose tissue is an important source of endogenous estrogen, and obesity is an important risk factor for endometrial cancer.⁶

It is essential to determine endometrial cancer's clinical and histopathological features for optimal treatment. The rates of pelvic and paraaortic lymph node metastasis in all patients diagnosed with endometrial cancer are 9% and 5%, respectively.⁷ Nowadays, systemic pelvic lymph node dissection has no proven benefit or harm at stage 1 endometrial carcinoma.⁸ But, many retrospective studies have shown that the role of systemic pelvic and para-aortic lymphadenectomy was to increase the survival of patients with moderate and high risk for lymph node metastasis.⁹

We aimed to analyse the prognostic factors in endometrioid adenocarcinoma and to evaluate the correlation between the characteristics of the tumour and survival.

MATERIALS AND METHODS

Ethics Committee Approval: This study was supported by Kocaeli University Scientific Research Projects Coordination Unit as KÜ GOKAEK 2018/9 scientific research project and approved by the ethics committee. (Date: 19.01.2018, decision no: 2018/9).

Material and Methods: The study included 206 patients with tumour histologic type Endometrioid Adenocarcinoma treated for endometrial cancer between May 2006 and May 2012 in Kocaeli University Faculty of Medicine, Department of Obstetrics and Gynecology. The data from 144 patients were accessed and incorporated into this study. The data was derived from the patient's pathology report. The demographic data, including age, diabetes mellitus (DM), hypertension (HT), parity, concomitant malignant disease, family history and smoking, were retrospectively evaluated from the records. At the same time, the pathology reports were examined to determine the surgical stages, tumour size, myometrial invasion, cervical involvement, adnexal involvement, peritoneal cytology, lymphovascular space invasion, and lymph node metastasis. The

patients were divided into two groups according to lymph node metastasis. The demographic data and tumour characteristics correlation between lymph node metastasis were evaluated. The factors affecting survival were analysed as multiple and single. Stage I grade 1-2 tumours were divided into two groups as performing lymphadenectomy or not, and 5-year survival was evaluated. The effects of lymphadenectomy on survival were compared between these two groups.

Statistical Analysis: All statistical analyses were performed using the IBM SPSS Statistics 20 statistical data program. Continuous variables were expressed as means with standard deviations or medians with quartiles, and categorical variables were expressed as frequencies and percentages. The significance of the difference between the groups was evaluated by Student's t-test. Categorical variables were assessed with Pearson's Chi-square test and Fisher's Exact Test. A p-value of <0.05 was considered statistically significant. The survival rate was estimated with Kaplan-Meier. The factors affecting survival outcomes were evaluated with the Cox Regression test. A p-value of <0.05 was considered statistically significant.

RESULTS

The study included 206 patients with tumour histologic type Endometrioid Adenocarcinoma who were treated for endometrial cancer between May 2006 and May 2012 in Kocaeli University Faculty of Medicine, Department of Obstetrics and Gynecology. The data from 144 patients were accessed and incorporated into this study.

The mean age of the patients was 58.51±10.15 years, and the mean BMI was 33.42±6.74. 29 (20.10%) of the patients were diagnosed in the premenopausal period, and 115 (79.9%) were diagnosed in the postmenopausal period. It was observed that 69 (47.9%) of the patients had HT, 39 (27.1%) had DM, and 15 (10.4%) were smokers. When the histopathological results of the patients were evaluated, 73 patients had grade 1 tumours, 58 had grade 2 tumours, and 13 had grade 3 tumours. When the patients were examined in terms of myometrial invasion, it was observed that the tumour was limited to the endometrium in 19 patients (12.5%), 98 patients (68.1%) had less than 1/2 and 28 patients (19.4%) had more than 1/2 myometrial invasion. Of the patients (n=99) in whom tumour size was reached in histopathology results, 27 (27.3%) had a tumour size below 2 cm, and 72 (72.7%) had a tumour size above 2 cm. Pelvic lymph node involvement was observed in 8 (7%) of 115 patients who underwent pelvic lymphadenectomy. Paraaortic lymph node involvement was observed in 2 of 48 patients (4.20%) who underwent

paraaortic lymphadenectomy. When the histopathology results were analysed, it was observed that lymphovascular invasion was present in 8 of 106 patients. The cervical stromal invasion was found in 1 patient (0.70%) and adnexal involvement in 10 patients (7.00%). Detailed characteristics of patients are shown in Table 1.

It was demonstrated that pelvic lymph node metastasis was observed in 5 (4.35%) patients with more than 1/2 of myometrial invasion. Therefore, the correlation between more than 1/2 of myometrial invasion and pelvic lymph node metastasis was consid-

ered as statistically significant (p=0.010). 3 (2.61%) patients had both adnexal metastasis and pelvic lymph node metastasis. Adnexal metastasis was associated with pelvic lymph node metastasis (p=0.015). There was a significant correlation between lymphovascular spread and pelvic lymph node metastasis (p=0.019). Lymph node metastasis was observed in 1 patient (5%) with a tumour size <2 cm and 6 (10%) patients with a tumour size ≥2 cm. There was no significant correlation between tumour size and pelvic lymph node metastasis (p=0.667) (Table 2).

Table 1. Characteristics of patients.

Characteristics		Statistical Data
Age, Mean ± SD		58.51 ± 10.15
Parity, Mean ± SD		2.98 ± 2.01
BMI, Mean ± SD		33.42 ± 6.74
Hypertension, n (%)		69 (47.90)
DM, n (%)		39 (27.10)
Smoking, n (%)		15 (10.40)
Menopause, n (%)	Premenopause	29 (20.10)
	Postmenopause	115 (79.90)
Tumour grade, n (%)	Grade 1	73 (50.70)
	Grade 2	58 (40.30)
	Grade 3	13 (9.00)
	-	19 (12.50)
Myometrial invasion, n (%)	Less than 1/2	98 (68.10)
	More than 1/2	28 (19.40)
	-	27 (27.30)
Tumour size, n (%)	Less than 2 cm	27 (27.30)
	More than 2 cm	72 (72.70)
Lymphovascular space invasion, n (%)	Negative	98 (92.50)
	Positive	8 (7.50)
Pelvic lymph node metastasis, n (%)	Negative	107 (93.00)
	Positive	8 (7.00)
Paraaortic lymph node metastasis, n (%)	Negative	46 (95.80)
	Positive	2 (4.20)
Cervical invasion, n (%)	Negative	122 (84.70)
	Stromal invasion	1 (0.70)
	Glandular invasion	21 (14.60)
Adnexal metastasis, n (%)	Negative	134 (93.10)
	Positive	10 (6.90)

BMI: Body mass index; DM: Diabetes Mellitus.

Table 2. Myometrial invasion, adnexal metastasis, lymphovascular space invasion, tumour size and pelvic lymph node metastasis.

Characteristics		Pelvic Lymph Node Metastasis		p*
		Negative, n (%)	Positive, n (%)	
Myometrial invasion	Less than 1/2	88 (76.5)	3 (2.61)	0.010
	More than 1/2	19 (16.52)	5 (4.35)	
Adnexal metastasis	Negative	101 (87.20)	5 (5.00)	0.015
	Positive	6 (5.21)	3 (2.61)	
Lymphovascular space invasion (n=80)	Negative	72 (90.00)	1 (1.25)	0.019
	Positive	5 (6.25)	2 (2.50)	
Tumour size (n=99)	Less than 2 cm	26 (26.26)	1 (1.01)	0.667
	More than 2 cm	66 (66.66)	6 (6.06)	

*: Fisher Exact Test

In this study, the 5-year survival rate was calculated as 87.4%. The graph of overall survival is shown in Figure 1a. Comparing age and survival was relatively significant when evaluated alone ($p=0.000$). The relationship between age and survival is shown in Figure 1b.

When survival outcomes were compared with menopause, DM, HT, and smoking, no significant correlation was observed with each other. Comparing age and survival was relatively significant when evaluated alone but was not found to be statistically significant in the multivariate analysis ($p=0.000$; $\text{Exp}(B)=1.09$). A significant correlation was found between myometrial invasion and survival, and myometrial invasion of less than 1/2 was observed to improve

survival by 8.74 times ($p=0.022$; $\text{Exp}(B)=8.74$). There was a significant correlation between grade and survival. Patients' survival with grade 1 tumours was found to be associated with 11.05 times better prognosis than grade 3 tumours ($p=0.023$; $\text{Exp}(B)=11.05$) (Table 3).

Patients with stage 1 grade 1-2 tumours were compared in terms of survival in two groups: 28 patients did not undergo lymphadenectomy, and 88 patients underwent lymphadenectomy. 5-year survival rate was 85.2% in patients without lymphadenectomy, and survival in the group with lymphadenectomy was 89.8%; no statistically significant difference was observed between them ($p=0.575$) (Table 4).

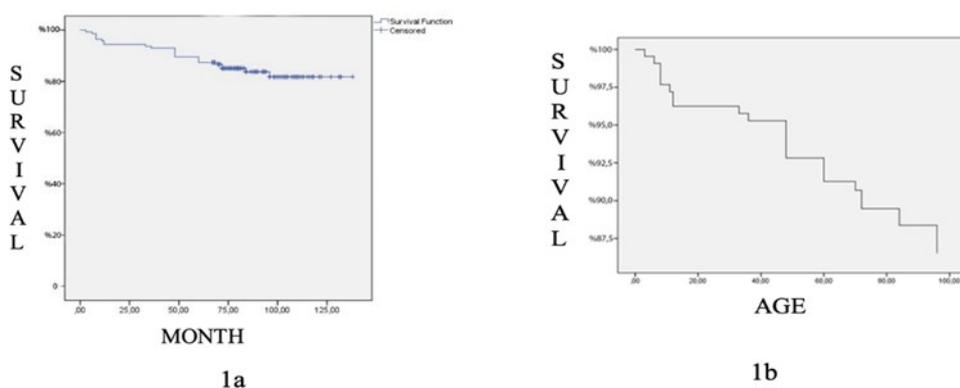


Figure 1. Survival rates. **1a:** Overall survival (Kaplan-Meier), **1b:** The relationship between age and survival rate (Kaplan-Meier).

Table 3. Factors related to survival rate.

Characteristics	p*	Relative Risk
Age	0.000	1.09
Menopause	0.074	-
DM	0.189	-
HT	0.349	-
Grade	0.023	11.05
Myometrial invasion	0.022	8.74
Pelvic lymph node involvement	0.606	-
Adnexal metastasis	0.712	-
Tumour size	0.305	-
Lymphovascular space invasion	0.573	-

DM: Diabetes Mellitus; HT: Hypertension; *: Cox regression analysis.

Table 4. Stage I Grade 1-2 tumours pelvic lymph node dissection and survival.

Stage I Grade 1-2 tumours	n (%)	5-year survival	p*
Lymph node	Dissection +	88 (75.9)	89.8%
	Dissection -	28 (24.1)	85.2%

*: Cox Regression Analysis.

DISCUSSION AND CONCLUSION

Endometrial cancer is typically a disease of the peri / post-menopausal period. The mean age at diagnosis was 63 years, and 90% of cases were above 50.¹⁰ In our study, the mean age of the patients was 58.51 ± 10.15 years. 9 (6.25%) patients were under the age of 40.

Ruterbusch et al.¹⁴ reported the effect of comorbid conditions and racial differences on the survival rates in patients with endometrial cancer. They reported that DM and obesity are not significantly associated with the risk of death due to endometrial cancer in both black and white women. However, they have shown that HT reduces the risk of death in both groups. McVicer et al.¹⁵ reported in a meta-analysis that death rates due to all causes were increased by 42%, and recurrent disease was increased by 23% in diabetic endometrial carcinoma patients. In our study, DM, HT, smoking, and BMI were not found to be significantly associated with survival in the uterine endometrioid adenocarcinoma.

Bak et al.¹⁶ compared grade 1 and grade 2 cases in a group of 171 low-risk endometrial cancer patients in their study and reported that there was a statistically significant difference in disease-free survival (97.5% - 79.3%), although no significant difference in overall survival. In the study of Han et al.¹⁷, the tumour grade was higher in Stage IB patients compared to Stage IA. They concluded that myometrial invasion in stage IA disease and the histological grade of the tumour in stage IB disease were associated with disease-free survival. Wang et al.¹⁸ have revealed in a meta-analysis that the presence of myometrial invasion of more than ½ is associated with worse survival outcomes. In our study, there was a significant correlation between grade and survival in endometrial cancer, which is consistent with the literature.

The ASTEC study²⁶ evaluated 1408 patients with endometrial cancer; 704 patients with lymphadenectomy and 704 patients without lymphadenectomy were compared. The 5-year overall survival rate was 81% in the group without lymphadenectomy and 80% in the lymphadenectomy group. Panici et al.²⁷ compared 264 patients with lymphadenectomy and 250 patients without lymphadenectomy. Early and late postoperative complications were more frequent in the lymphadenectomy group. The 5-year disease-free and overall survival rates were similar in two groups; in patients who underwent lymphadenectomy rates were 81-85.9%; without lymphadenectomy were 81.7-90%. In a study by Zhang et al.,²⁸ patients with endometrial cancer who underwent surgery were investigated. It was concluded that lymphadenectomy may be avoided in patients with low risk. In our study, patients with Stage 1 grade 1-2 tumours, 28 patients who underwent lymphadenectomy without lymphadenectomy and 88 patients who

underwent lymphadenectomy were compared in terms of survival. In patients without lymphadenectomy, 5-year survival was 85.2%, and the survival rate was 89.8% in patients with lymphadenectomy. No statistically significant difference was observed between them. Our study was found to be compatible with the literature. The missing aspects of our study; the number of patients with advanced stage and lymph node metastasis is low, and cervical involvement was present in only 1 patient. On the other hand, since most of the study patients had stage I tumours, this study provides information about the effect of lymphadenectomy on survival in stage I grade 1-2 tumours.

Endometrial cancer is an important cause of morbidity and mortality among women. Therefore, it is important to determine the risk factors of the disease, to determine the prognostic factors and to standardise the treatment modality.

In conclusion, we found in our study that myometrial invasion, adnexal metastasis and lymphovascular spread were prognostic factors for lymph node metastasis which is an important prognostic factor for endometrial cancer. Our findings were consistent with the current literature. When the factors affecting survival are investigated; we determined that myometrial invasion, grade and age of diagnosis are important prognostic factors for endometrial adenocarcinoma. We concluded that lymphadenectomy does not increase the survival rate in stage I grade 1-2 tumours. Thus, the morbidity of lymphadenectomy to the patient can be avoided. Treatment should be individualised according to the patient's condition when the decision is made for lymphadenectomy.

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